

## Vandetanib in Patients With Locally Advanced or Metastatic Medullary Thyroid Cancer: A Randomized, Double-Blind Phase III Trial

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### A B S T R A C T

#### Purpose

There is no effective therapy for patients with advanced medullary thyroid carcinoma (MTC). Vandetanib, a once-daily oral inhibitor of RET kinase, vascular endothelial growth factor receptor, and epidermal growth factor receptor signaling, has previously shown antitumor activity in a phase II study of patients with advanced hereditary MTC.

#### Patients and Methods

Patients with advanced MTC were randomly assigned in a 2:1 ratio to receive vandetanib 300 mg/d or placebo. On objective disease progression, patients could elect to receive open-label vandetanib. The primary end point was progression-free survival (PFS), determined by independent central Response Evaluation Criteria in Solid Tumors (RECIST) assessments.

#### Results

Between December 2006 and November 2007, 331 patients (mean age, 52 years; 90% sporadic; 95% metastatic) were randomly assigned to receive vandetanib (231) or placebo (100). At data cutoff (July 2009; median follow-up, 24 months), 37% of patients had progressed and 15% had died. The study met its primary objective of PFS prolongation with vandetanib versus placebo (hazard ratio [HR], 0.46; 95% CI, 0.31 to 0.69;  $P < .001$ ). Statistically significant advantages for vandetanib were also seen for objective response rate ( $P < .001$ ), disease control rate ( $P = .001$ ), and biochemical response ( $P < .001$ ). Overall survival data were immature at data cutoff (HR, 0.89; 95% CI, 0.48 to 1.65). A final survival analysis will take place when 50% of the patients have died. Common adverse events (any grade) occurred more frequently with vandetanib compared with placebo, including diarrhea (56% v 26%), rash (45% v 11%), nausea (33% v 16%), hypertension (32% v 5%), and headache (26% v 9%).

#### Conclusion

Vandetanib demonstrated therapeutic efficacy in a phase III trial of patients with advanced MTC (ClinicalTrials.gov NCT00410761).

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### INTRODUCTION

Medullary thyroid carcinoma (MTC), a malignancy of the parafollicular C cells of the thyroid gland, accounts for approximately 5% of all thyroid cancers and presents either sporadically (75% of patients) or in a hereditary pattern.<sup>1,2</sup> The 10-year overall survival rate in unselected patients with MTC is approximately 75%, but it decreases to 40% or less in patients with locally advanced or metastatic disease.<sup>1,3,4</sup> Neither radiotherapy nor chemotherapy has demonstrated durable objective responses in patients with advanced MTC.<sup>5,6</sup>

Germline mutations in the *RET* (rearranged during transfection) proto-oncogene occur in virtually all patients with hereditary MTC.<sup>7-9</sup> Approximately 50% of patients with sporadic MTC have somatic *RET* mutations, and 85% of them have the *M918T* mutation.<sup>10,11</sup> Evidence from preclinical studies of molecular targeted therapeutics with activity against *RET* demonstrate that RET kinase is a potential therapeutic target in MTC.<sup>12-14</sup> Other signaling pathways likely to contribute to the growth and invasiveness of MTC include vascular endothelial growth factor receptor (VEGFR)–dependent tumor angiogenesis and

epidermal growth factor receptor (EGFR)–dependent tumor cell proliferation.<sup>15</sup>

Vandetanib is a once-daily oral agent that selectively targets RET, VEGFR, and EGFR signaling.<sup>12,16</sup> We report the results of an international, randomized, placebo-controlled, double-blind, phase III study (ZETA) to evaluate vandetanib 300 mg/d in patients with locally advanced or metastatic MTC.

## PATIENTS AND METHODS

### Eligibility

Eligible patients were adults who had measurable, unresectable locally advanced or metastatic, hereditary or sporadic MTC. Submission of a tumor sample was required except for patients with hereditary MTC who had a documented germline *RET* mutation. Other key inclusion criteria were WHO performance status of 0 to 2 and serum calcitonin level  $\geq 500$  pg/mL. Exclusion criteria included significant cardiac, hematopoietic, hepatic, or renal dysfunction and administration of chemotherapy and/or radiation therapy within 4 weeks before random assignment. All patients provided written informed consent. The protocol was approved by all relevant institutional ethical committees or review bodies, and the study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice, and the AstraZeneca policy on bioethics.

### Study Design and Treatments

Patients recruited to this multicenter phase III study were randomly assigned in a 2:1 ratio to receive oral vandetanib at a starting dose of 300 mg/d or placebo until disease progression. On objective disease progression based on investigator assessment, patients discontinued study treatment, were unblinded, and could elect to enter postprogression, open-label treatment with vandetanib until a withdrawal criterion was met. All patients were to be followed for survival.

The primary objective was to determine whether vandetanib, compared with placebo, prolonged progression-free survival (PFS) on the basis of independent central review. Secondary assessments included objective response rate, disease control rate at 24 weeks, duration of response, overall survival, biochemical response (decreases in serum levels of calcitonin and carcinoembryonic antigen [CEA]), and time to worsening of pain (for time to worsening of pain, see Methods and Results in the Appendix, online only).

The principal investigator in collaboration with the study sponsor, AstraZeneca, designed the clinical trial. The sponsor provided funding and organizational support, collected and managed the data, and performed the statistical analysis. Each author reviewed and approved the manuscript and the principal investigator had final responsibility for the decision to submit for publication. The senior academic authors developed the manuscript, and all coauthors contributed to the manuscript.

### Efficacy

PFS was determined from objective tumor measurements performed at screening and then every 12 weeks until progression or withdrawal of consent.

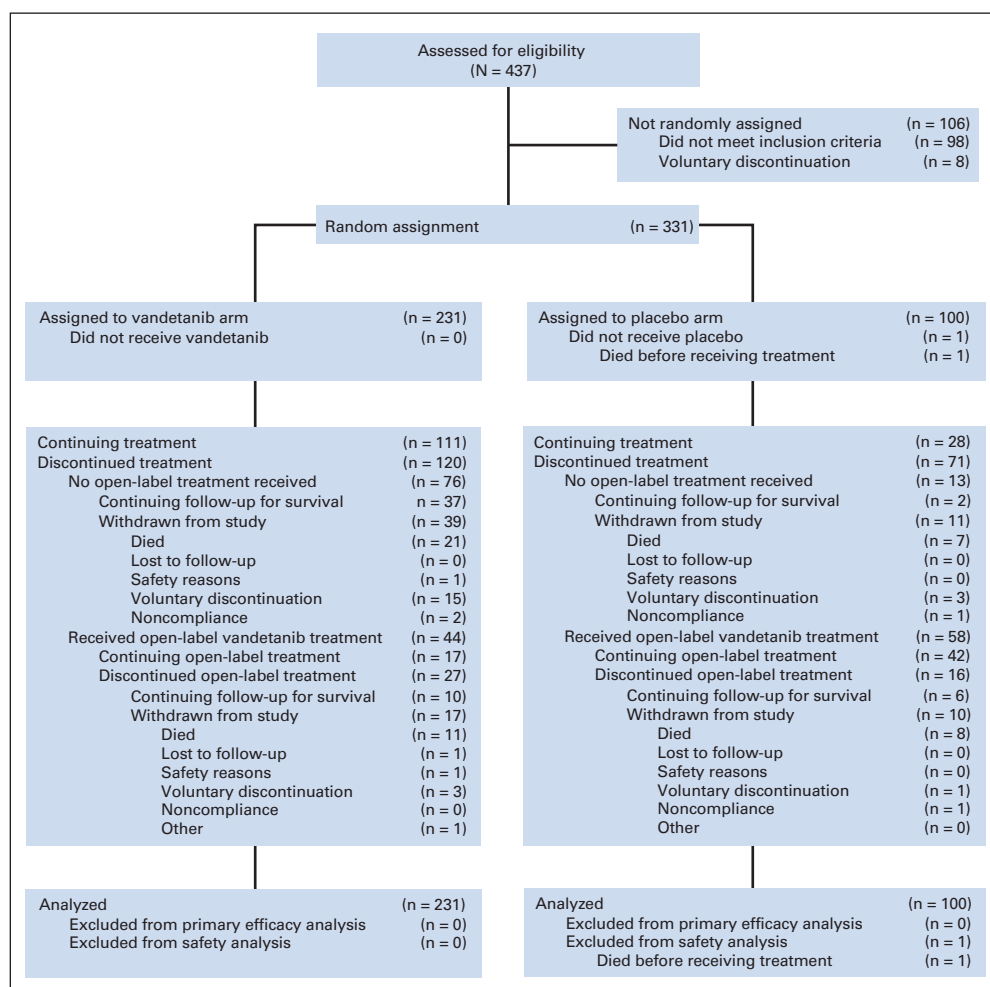


Fig 1. CONSORT diagram.

Tumor assessments were categorized by the investigator by using Response Evaluation Criteria in Solid Tumors v1.0 (RECIST).<sup>17</sup> Responses were confirmed by central review of separate assessments performed at least 4 weeks apart. RECIST assessments derived from an independent central review of patient scans were the basis for the primary analysis. If, according to central review, progression had not occurred by the time a patient entered open-label treatment, open-label RECIST assessments were also used in the derivation of PFS, objective response rate, disease control rate, and duration of response. PFS was defined from the date of random assignment to the date of objective progression or death (by any cause in the absence of progression within 3 months of the last evaluable RECIST assessment). Patients who had not progressed or who had died at the time of analysis were censored at the time of their last evaluable RECIST assessment.

Overall survival was calculated from the date of random assignment to the date of death with patients followed every 12 weeks until withdrawal of consent or death. Patients who had not died at the time of analysis were censored at the time they were last known to be alive. A final analysis of overall survival is planned when 50% of the study patients have died.

### RET Mutational Status

The presence of an *RET* mutation was determined by a combination of two methods: (1) an amplification-refractory mutation system (ARMS) assay that specifically detects the most common *RET* mutation (*M918T*) found in sporadic MTC, and (2) direct DNA sequencing following polymerase chain reaction amplification of *RET* (exons 10, 11, and 13 to 16). A

mutation-positive sample had either *M918T* by ARMS assay or an *RET* mutation in any of exons 10, 11, and 13 to 16. Conversely, a mutation-negative sample had no *M918T* mutation by ARMS and a wild-type *RET* sequence in each of exons 10, 11, and 13 to 16. The mutation status was declared unknown in cases in which an assay failed to yield a sequence at any of the tested exons (by sequencing or ARMS assay), and none of the successful assays demonstrated a mutation.

### Measurement of Serum Tumor Markers

Blood samples for calcitonin and CEA analysis were collected at baseline (day 1), every 4 weeks until week 12, and then every 12 weeks thereafter. Serum levels of calcitonin and CEA were determined as previously described.<sup>18</sup> A patient's best biochemical response for either calcitonin or CEA was defined as follows: complete response, normalization of serum levels following treatment confirmed a minimum of 4 weeks later; partial response,  $\geq 50\%$  decrease from baseline levels maintained over a minimum of 4 weeks; stable disease, between  $+50\%$  and  $-50\%$  change from baseline levels maintained for at least 4 weeks; and progressive disease,  $\geq 50\%$  increase from baseline maintained for at least 4 weeks.

### Safety and Tolerability

Safety was assessed throughout the study by monitoring and recording adverse events, 12-lead ECG parameters, vital signs, clinical chemistry, hematology, and urinalysis. Adverse events were assessed by using the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE, v3). Scheduled 12-lead ECGs were performed during screening, at 1, 2, 4, 8, and 12 weeks and every 3 months thereafter. The QTc interval was evaluated centrally, and prolongation was defined as a single measurement of  $\geq 550$  ms or an increase of  $\geq 100$  ms from baseline, two consecutive measurements (within 48 hours of each other) that were  $\geq 500$  ms but less than 550 ms, or an increase of  $\geq 60$  ms but less than 100 ms from baseline to a value  $\geq 480$  ms. Specific dose reduction plans were in place for management of skin toxicity, GI toxicity, and QTc prolongation. There was also a general dose reduction scheme for any CTCAE grade 3 or 4 adverse event (patients started at vandetanib 300 mg/d or placebo, and dose was reduced to 200 mg/d for a grade 3 or 4 adverse event; if further grade 3 or 4 toxicity occurred, reduction to 100 mg/d was allowed).

### Statistical Analysis

The study was designed to have more than 80% power to detect a hazard ratio (HR) less than 0.50 at a 5% significance level; a minimum of 90 progression events were required, assuming a median PFS of 12 months in the placebo group and an overall sample size of 232 patients. Analyses of PFS and overall survival were conducted by using the log-rank test (unadjusted model with treatment factor only) in the intention-to-treat population. A sensitivity analysis of PFS was performed by using Cox's proportional hazards regression model, which allowed for the effect of treatment and included terms for *RET* mutation status, MTC status (hereditary or sporadic), prerandomization historic calcitonin and CEA changes, number of prior therapies, and response to prior therapy.<sup>19</sup> The following predefined sensitivity analyses were also performed for PFS: per protocol that excluded significant protocol deviators; Whitehead method to assess the impact of a differential frequency of assessments in the two treatment arms; randomized phase alone (ie, excluding the open-label phase); and PFS derived from investigator assessments.<sup>20</sup> The objective response rate and disease control rate were analyzed by using logistic regression (these variables included open-label assessments). All *P* values were two-sided. Subgroup analyses of PFS by prespecified baseline characteristics and ad hoc subgroup analyses of PFS and objective response rate by *RET* mutation status and *M918T* mutation status were performed.

## RESULTS

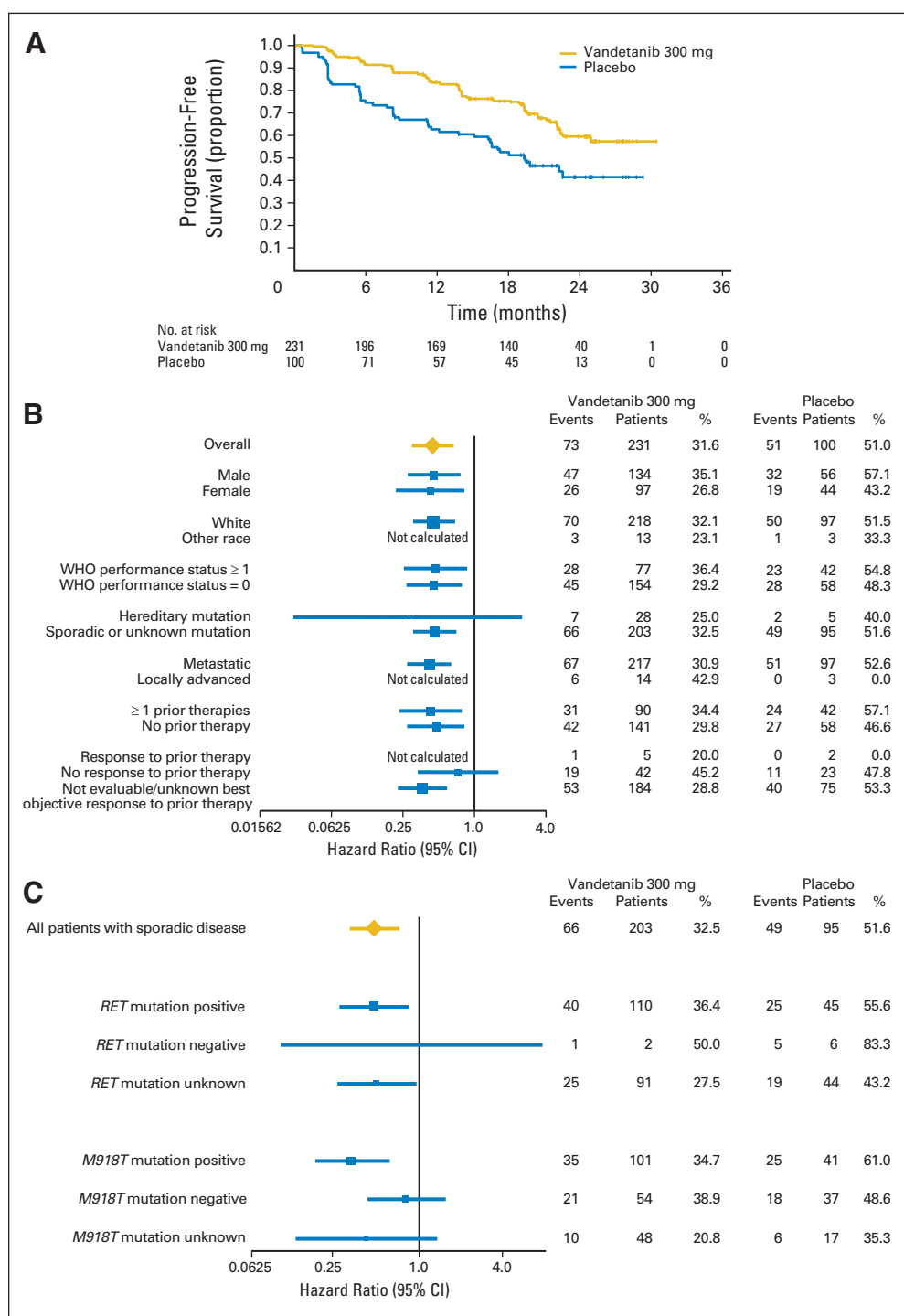
### Patients

Between December 7, 2006, and November 21, 2007, 331 patients recruited from 23 countries were randomly assigned to vandetanib (231) or placebo (100; Fig 1). Although not an exact 2:1

**Table 1.** Baseline Demographics and Patient Characteristics (intention-to-treat population; all randomly assigned patients)

| Characteristic                                | Vandetanib<br>(300 mg)<br>(n = 231) |    | Placebo<br>(n = 100) |    |
|---|-------------------------------------|----|----------------------|----|
|   | No.                                 | %  | No.                  | %  |
| Sex   |                                     |    |                      |    |
| Male  | 134                                 | 58 | 56                   | 56 |
| Female  | 97                                  | 42 | 44                   | 44 |
| Mean age, years                               | 50.7                                |    | 53.4                 |    |
| WHO performance status                        |                                     |    |                      |    |
| 0   | 154                                 | 67 | 58                   | 58 |
| 1   | 67                                  | 29 | 38                   | 38 |
| 2   | 10                                  | 4  | 4                    | 4  |
| Disease type                                  |                                     |    |                      |    |
| Hereditary                                    | 28                                  | 12 | 5                    | 5  |
| Sporadic or unknown                           | 203                                 | 88 | 95                   | 95 |
| Locally advanced                              | 14                                  | 6  | 3                    | 3  |
| Metastatic                                    | 217                                 | 94 | 97                   | 97 |
| Hepatic                                       | 154                                 | 67 | 64                   | 64 |
| Lymph nodes                                   | 135                                 | 58 | 68                   | 68 |
| Respiratory                                   | 126                                 | 54 | 60                   | 60 |
| Bone/locomotor                                | 78                                  | 34 | 40                   | 40 |
| Neck  | 33                                  | 14 | 17                   | 17 |
| No. of organs involved<br>(excluding thyroid) |                                     |    |                      |    |
| 0 or 1  | 29                                  | 13 | 8                    | 8  |
| $\geq 2$                                      | 202                                 | 87 | 92                   | 92 |
| Prior systemic therapy for<br>MTC             |                                     |    |                      |    |
| 0   | 141                                 | 61 | 58                   | 58 |
| $\geq 1$                                      | 90                                  | 39 | 42                   | 42 |
| <i>RET</i> mutation                           |                                     |    |                      |    |
| Positive                                      | 137                                 | 59 | 50                   | 50 |
| Negative                                      | 2                                   | 1  | 6                    | 6  |
| Unknown                                       | 92                                  | 40 | 44                   | 44 |

Abbreviations: MTC, medullary thyroid cancer; *RET*, rearranged during transfection.



**Fig 2.** (A) Kaplan-Meier curve of progression-free survival (PFS; intention-to-treat population; all randomly assigned patients); derived from all available centralized Response Evaluation Criteria in Solid Tumors (RECIST) assessments. (B) Forest plot of hazard ratios for PFS according to baseline characteristics and disease status. (C) Forest plot of hazard ratios for PFS according to rearranged during transfection (*RET*) mutation status and *M918T* mutation status in patients with sporadic medullary thyroid carcinoma. (B, C) A hazard ratio < 1 favors vandetanib. The analyses were performed using a log-rank test with treatment as the only factor.

randomization, this imbalance occurred by chance. Patient characteristics and baseline demographics were similar in both arms (Table 1). The majority of patients presented with sporadic disease, and most had metastatic disease at study entry. At data cutoff (July 31, 2009), the median duration of follow-up was 24 months, and 139 patients were

continuing blinded treatment: 111 (48%) randomly assigned to vandetanib and 28 (28%) randomly assigned to placebo. Among 123 patients who developed tumor progression and were eligible to receive open-label treatment, 93 (vandetanib, 41 of 67 [61%]; placebo, 52 of 56 [93%]) elected to enter postprogression open-label treatment with

vandetanib. Overall, 48 deaths (32, vandetanib arm; 16, placebo arm) occurred at the time of data cutoff, including one patient randomly assigned to the placebo arm who died of progressive MTC before receiving study treatment and who was not included in the safety analysis population. All patients were included in the efficacy analysis.

### Efficacy

At the time of analysis, 124 patients (37%) had progressed and 48 (15%) had died. Significant prolongation of PFS was observed for patients receiving vandetanib compared with placebo (HR, 0.46; 95% CI, 0.31 to 0.69;  $P < .001$ ; Fig 2A; Table 2). The median PFS was 19.3 months in the placebo group and, although the median had not yet been reached for the vandetanib group, fitting a Weibull model indicated a predicted median of 30.5 months.<sup>21</sup> The PFS at 6 months was 83% (vandetanib) and 63% (placebo). The Kaplan-Meier plot indicates that the relative hazards were larger at earlier time points. In addition to the primary analysis, Cox regression analysis as well as other sensitivity analyses detected an improvement in PFS with vandetanib versus placebo (Table 2). A total of 51 patients (23 vandetanib, 28 placebo) received open-label vandetanib before progression by central read was documented. Both visual inspection of the forest plot and the finding of a lack of statistical significance for the planned global interaction test ( $P = .177$ ) suggest that the PFS benefits observed were generally consistent across all prespecified subgroups (Fig 2B).

Vandetanib also showed significant advantages compared with placebo in the secondary efficacy end points of objective response rate, disease control rate, and calcitonin and CEA biochemical response rates (Table 2). Objective responses were durable on the basis of the median duration of response not being reached at 24 months of follow-up (fitting a Weibull model gives a predicted median duration of response of 22 months). It is important to note that 12 of 13

responses observed in patients initially randomly assigned to placebo occurred while the patients were subsequently receiving vandetanib in the open-label phase. Overall survival data were immature at data cutoff (HR, 0.89; 95% CI, 0.48 to 1.65; Fig 3). A final survival analysis will take place when 50% of the patients have died.

Of the 33 patients with hereditary MTC, 32 had a documented *RET* germline mutation before study entry, and of the 28 receiving vandetanib, 13 (46.4%) had an objective response. Paraffin blocks or slides were available for analysis from 297 of 298 patients with sporadic MTC. An *RET* mutation was present in 155 patients (52.0%), no *RET* mutation was present in eight patients (2.7%), and the *RET* mutation status was unknown in 135 patients (45.3%). There was a high number of patients with unknown *RET* mutation status because their paraffin blocks or slides had an insufficient quantity or quality of DNA for complete analysis. The small number of *RET*-negative patients means that subgroup analyses of PFS (Fig 3B) and objective response rate (Table 3) by *RET* mutation status are inconclusive. In patients with sporadic MTC, however, a subgroup analysis of PFS by *M918T* mutation suggested that *M918T* mutation-positive patients had a higher response rate to vandetanib compared with *M918T* mutation-negative patients (Fig 2C; Table 3).

### Safety and Tolerability

The median duration of treatment in the randomized phase was 90.1 weeks (vandetanib) and 39.9 weeks (placebo). Common adverse events (any grade and grade 3 or higher) are summarized in Table 4. Thirty-one patients discontinued treatment during the randomized phase because of an adverse event: 28 (12%) receiving vandetanib and three (3%) receiving placebo. Adverse events such as diarrhea, rash, nausea, and hypertension occurred in more than 30% of patients receiving vandetanib; adverse events leading to discontinuation of vandetanib reported in more than 1% of patients were asthenia (1.7%)

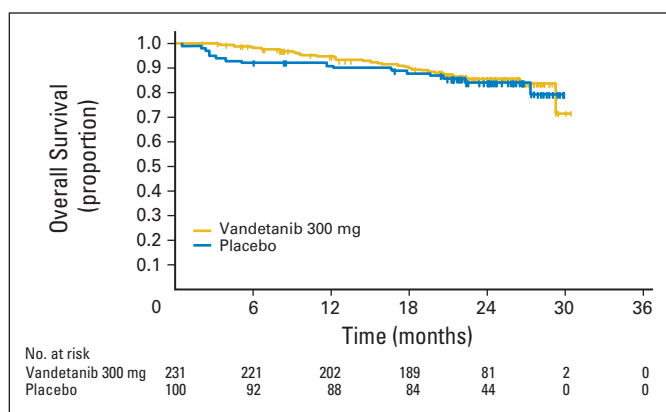
**Table 2.** Summary of Efficacy Results

| Progression-Free Survival            | Vandetanib                        |    | Placebo                           |    | HR   | OR   | 95% CI        | <i>P</i> |
|--------------------------------------|-----------------------------------|----|-----------------------------------|----|------|------|---------------|----------|
|                                      | No. of Events/<br>No. of Patients | %  | No. of Events/<br>No. of Patients | %  |      |      |               |          |
| Primary analysis                     | 73/231                            |    | 51/100                            |    | 0.46 |      | 0.31 to 0.69  | < .001   |
| Predefined sensitivity analyses      |                                   |    |                                   |    |      |      |               |          |
| Cox proportional hazards model       | 73/231                            |    | 51/100                            |    | 0.46 |      | 0.32 to 0.68  | < .001   |
| Per protocol analysis                | 71/215                            |    | 48/91                             |    | 0.45 |      | 0.30 to 0.68  | < .001   |
| Whitehead's method                   | 73/231                            |    | 51/100                            |    | 0.51 |      | 0.35 to 0.72  | < .001   |
| Excluding data from open-label phase | 64/231                            |    | 59/100                            |    | 0.27 |      | 0.18 to 0.41  | < .001   |
| Investigator RECIST assessments      | 101/231                           |    | 62/100                            |    | 0.40 |      | 0.27 to 0.58  | < .001   |
| Secondary efficacy end points        |                                   |    |                                   |    |      |      |               |          |
| Objective response rate              |                                   | 45 |                                   | 13 |      | 5.48 | 2.99 to 10.79 | < .001   |
| Disease control rate                 |                                   | 87 |                                   | 71 |      | 2.64 | 1.48 to 4.69  | .001     |
| Calcitonin biochemical response rate |                                   | 69 |                                   | 3  |      | 72.9 | 26.2 to 303.2 | < .001   |
| CEA biochemical response rate        |                                   | 52 |                                   | 2  |      | 52.0 | 16.0 to 320.3 | < .001   |

NOTE. Progression-free survival sensitivity analyses: An HR of < 1 favors vandetanib; all analyses were conducted by using log-rank test, except for Cox model; all analyses used data derived from centralized RECIST assessments, except for analysis based on investigator RECIST assessments; analysis based on investigator RECIST assessments excludes (censors) data from open-label phase since baseline was reset; for analysis excluding open-label phase, progression dates were imputed for patients who had evidence of progressing disease but had not yet reached a RECIST-defined objective progression at the time of entry into the open-label phase; covariates for Cox model were *RET* mutation status (positive, negative, unknown), calcitonin doubling time ( $\leq 24$  months,  $> 24$  months, unknown), CEA doubling time ( $\leq 24$  months,  $> 24$  months, unknown), number of prior systemic anticancer therapies ( $\geq 1$ , 0), response to most recent systemic anticancer therapy (complete response/partial response, stable disease/progressive disease, not evaluable/unknown), and MTC status (hereditary, sporadic/unknown). Secondary efficacy end points: An OR > 1 favors vandetanib.

Abbreviations: CEA, carcinoembryonic antigen; HR, hazard ratio; MTC, medullary thyroid cancer; OR, odds ratio; RECIST, Response Evaluation Criteria in Solid Tumors; *RET*, rearranged during transfection.





**Fig 3.** Kaplan-Meier curve of overall survival (intention-to-treat population; all randomly assigned patients).

and rash (1.3%). More patients required dose reduction of vandetanib compared with placebo for adverse events or QTc prolongation (35% *v* 3%). Nineteen patients (8%) developed protocol-defined QTc prolongation, but there were no reports of torsades de pointes. From entry, more patients on vandetanib compared with placebo were noted to have rising thyroid-stimulating hormone serum levels, and they required an increase in thyroid replacement (49.3% *v* 17.2%). Five patients on the vandetanib arm experienced adverse events leading to death during the randomized phase; these were single instances of aspiration pneumonia, respiratory arrest, respiratory failure, staphylococcal sepsis, and arrhythmia and acute cardiac failure in one patient. The two deaths due to an adverse event in the placebo arm were isolated cases of gastroenteritis and GI hemorrhage.

**Table 3.** Objective Response Rate: Summary of Subgroup Analyses (randomized phase)

| Patient Subgroup and Randomized Treatment | No. of Patients | Responses |      |
|---|-----------------|-----------|------|
|   |                 | No.       | %    |
| Hereditary MTC                            |                 |           |      |
| Vandetanib, 300 mg                        | 28              | 13        | 46.4 |
| Placebo                                   | 5               | 0         |      |
| Sporadic <i>RET</i> mutation positive     |                 |           |      |
| Vandetanib, 300 mg                        | 110             | 57        | 51.8 |
| Placebo                                   | 45              | 0         |      |
| Sporadic <i>RET</i> mutation negative     |                 |           |      |
| Vandetanib, 300 mg                        | 2               | 0         |      |
| Placebo                                   | 6               | 0         |      |
| Sporadic <i>RET</i> mutation unknown      |                 |           |      |
| Vandetanib, 300 mg                        | 91              | 31        | 34.1 |
| Placebo                                   | 44              | 1         | 2.3  |
| Sporadic <i>M918T</i> mutation positive   |                 |           |      |
| Vandetanib, 300 mg                        | 101             | 55        | 54.5 |
| Placebo                                   | 41              | 0         |      |
| Sporadic <i>M918T</i> mutation negative   |                 |           |      |
| Vandetanib, 300 mg                        | 55              | 17        | 30.9 |
| Placebo                                   | 39              | 1         | 2.6  |
| Sporadic <i>M918T</i> mutation unknown    |                 |           |      |
| Vandetanib, 300 mg                        | 48              | 16        | 33.3 |
| Placebo                                   | 17              | 0         |      |

Abbreviations: MTC, medullary thyroid cancer; *RET*, rearranged during transfection.

**Table 4.** Common Adverse Events (safety population)

| Adverse Event  | Vandetanib (300 mg) (n = 231) |     | Placebo (n = 99) |    |
|--|-------------------------------|-----|------------------|----|
|  | No.                           | %   | No.              | %  |
| Any grade occurring with an incidence $\geq 10\%$ overall        |                               |     |                  |    |
| Diarrhea   | 130                           | 56  | 26               | 26 |
| Rash   | 104                           | 45  | 11               | 11 |
| Nausea   | 77                            | 33  | 16               | 16 |
| Hypertension   | 73                            | 32  | 5                | 5  |
| Fatigue  | 55                            | 24  | 23               | 23 |
| Headache   | 59                            | 26  | 9                | 9  |
| Decreased appetite   | 49                            | 21  | 12               | 12 |
| Acne   | 46                            | 20  | 5                | 5  |
| Asthenia   | 34                            | 14  | 11               | 11 |
| Vomiting   | 34                            | 14  | 7                | 7  |
| Back pain  | 21                            | 9   | 20               | 20 |
| Dry skin   | 35                            | 15  | 5                | 5  |
| Insomnia   | 30                            | 13  | 10               | 10 |
| Abdominal pain   | 33                            | 14  | 5                | 5  |
| Dermatitis acneiform   | 35                            | 15  | 2                | 2  |
| Cough  | 25                            | 10  | 10               | 10 |
| Nasopharyngitis  | 26                            | 11  | 9                | 9  |
| ECG QT prolonged*  | 33                            | 14  | 1                | 1  |
| Weight decreased   | 24                            | 10  | 9                | 9  |
| Grade 3+ occurring with an incidence of $\geq 2\%$ on either arm |                               |     |                  |    |
| Diarrhea   | 25                            | 11  | 2                | 2  |
| Hypertension   | 20                            | 9   | 0                |    |
| ECG QT prolonged*  | 18                            | 8   | 1                | 1  |
| Fatigue  | 13                            | 6   | 1                | 1  |
| Decreased appetite   | 9                             | 4   | 0                |    |
| Rash   | 8                             | 4   | 1                | 1  |
| Asthenia   | 6                             | 3   | 1                | 1  |
| Dyspnea  | 3                             | 1   | 3                | 3  |
| Back pain  | 1                             | 0.4 | 3                | 3  |
| Syncope  | 0                             |     | 2                | 2  |

\*As defined according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, v3 (see Results for the incidence of protocol-defined QTc prolongation as described in Methods, Safety and Tolerability).

## DISCUSSION

Patients with locally advanced or metastatic MTC are incurable, and chemotherapy and radiation therapy have been largely ineffective. Therefore, the ability to substantially prolong the time to disease progression would benefit such patients. Mutations in the *RET* proto-oncogene are central to the development of MTC in virtually all patients with hereditary MTC and in approximately half the patients with sporadic MTC.<sup>7-9,11</sup> Following preclinical studies demonstrating that vandetanib inhibited signaling through RET kinase,<sup>12,22</sup> a phase II clinical trial of oral vandetanib (300 mg) was initiated in patients with locally advanced or metastatic hereditary MTC. There were confirmed partial remissions in 20% of patients and stable disease of more than 24 weeks in 73% of patients.<sup>18</sup> Published reports of early-phase clinical trials of other tyrosine kinase inhibitors in patients with advanced MTC have shown partial remission rates ranging from 0% to 25% in small single-arm trials.<sup>23-29</sup>

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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